End of Life Care and Dementia 2022

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Objectives

At the end of this session, the participant will be able to:
- describe approaches to identifying persons who are near end of life
- describe the natural history of mild cognitive impairment
- describe recent approaches to managing persons with dementia

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End of Life Care

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Surprise Question to identify patients who will die in the next year (1)

- Prospective cohort of 3640 patients recruited from 2 Dutch primary care practices
  - The clinicians identified 67 for whom they would respond "no" to the "Surprise Question"
  - Mined the EMR and found 501 for whom the Supportive and Palliative Care Indicators Tool (SPICT) indicated a potential need to palliative care (101 of whom the clinicians agreed)
- One year later, 36 had died, 10 of whom died suddenly

	Se	Sp	LR+	LR-
SQ	.50	.99	50	0.50
SPICT	.58	.98	29	0.43

- The clinicians found the SPICT to be burdensome

Van Wijmen, Fam Pract 2020

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Lower costs and healthcare utilization with hospital care at home (2)

- RCT of 91 adults in ER needing admission:
  - infection, CHF, COPD, asthma, CKD requiring diuresis, diabetic complications, acute gout, hypertensive urgency, previously diagnosed a fib with RVR, anticoagulation needs, or patients at end-of-life desiring medical management only
  - Home care consisted of 1 daily visit by internist and 2 daily nurse visits and additional needed visits 24 hours daily.
  - Specialty consultants via telemed; RT, PT, labs, x-ray, IV meds, etc. also available as needed
- Participants were chronically ill, frail, and over 80 years of age
- Hospital at home:
  - 38% lower costs; fewer tests and consultations
  - Less time sedentary or lying down
  - LOS was sl higher ((4.5 days vs 3.8 days) but had fewer readmissions (7% vs. 23%)

Levine, Ann Int Med 2020

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Online module promotes advance directives documentation (3)

- RCT of 986 (English or Spanish speaking) primary care patients
  - mean age 63 with 2 or more chronic conditions
  - 40% had low health literacy
  - Randomized to receive an advanced directive form or to the form + online module (PREPARE; https://prepareforyourcare.org/welcome)
- 15 months of follow-up
- Completion of advanced directive 33.1% of paper only compared with 43% of combined intervention (NNT=10)
- Not part of the study, but 5 Wishes is available in 27 languages (https://fivewishes.org/)

Sudore, JAMA Int Med 2018

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Advance care planning increases advance directives and surrogate decision-maker assignment (4)

- Cluster RCT
  - 16 clusters (nursing homes or home care) and 201 participants in mid 80s
  - Usual care vs. advanced care planning education (trained facilitators and educational materials and tools)
  - After 1 year
    - Completion of advanced directive 34% vs. 93% (NNT=2)
    - Identification of surrogate decision-maker 67% vs. 94% (NNT=4)
  - Effective but time consuming (average 2 hours)

Overbeek, JAGS 2018

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If you ask patients about their preferred place of death, they will tell you (5)

- Part of a larger RCT. Control group (n=230) was evaluated 4 times during the 6 months after hospitalization
- Participants were asked about PPD
  - Baseline 48% had no PPD
  - Patients with prior admissions preferred to die at home
  - Patients with more chronic illnesses preferred to die in a health care facility
  - Half changed their preference
- Bottom line – ask and ask often!

Van Doorne, Age Ageing 2021

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Hospital-based specialist palliative care (6)

- Cochrane SR
  - Hospital-based specialist palliative care (HSPC) vs. usual care
  - 42 RCTs with 6678 patients and 1101 caregivers/family members
  - 21 studies enrolled persons with cancer, 6 with CHF
  - 40 studies had high risk of bias in at least one area
- HSPC vs. usual care
  - Sl improvement in HRQOL (SMD 0.26)
  - Sl decreased symptom burden (SMD -0.26)
  - Sl increased satisfaction with care (SMD 0.36)
  - More likely to die at home (OR 1.63)
  - No difference in pain, adverse events, or caregiver burden
  - Economic studies were all over the place

Bajwah, Cochrane 2020

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Subcutaneous scopolamine butylbromide reduces the death rattle in dying patients (SILENCE) (7)

- RCT in Netherlands inpatient hospice with 157 actively dying persons
  - scopolamine butylbromide 20 mg SQ four times daily vs. placebo
- Continued until the person died or until the occurrence of death rattle heard 2 feet away twice during a 6-hour interval
- Scopolamine vs. placebo
  - Death rattle less frequent (13% vs. 27%)
  - No difference in restlessness, dry mouth, urinary retention
- Not available in US

Van Esch, JAMA 2021

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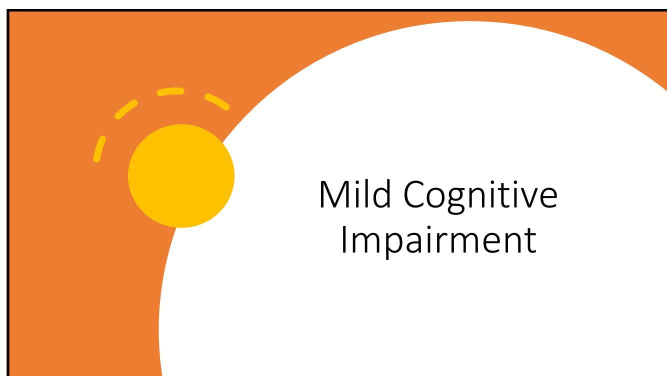

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AAN guideline for patients with MCI (8)

- SRs with 62 studies
  - variability in definition of MCI
  - Variable outcome measures, study duration
- best guess is that MCI becomes more prevalent with advancing age
- between 15% and 38% of patients with MCI regress to normal
- Pharmacologic therapy (limited number of studies)
  - Donepezil (3 studies) galantamine (2 studies), rivastigmine (1 study) – unlikely to slow progression to dementia
  - Many other "non-traditional" medications with single studies and were either ineffective or too short duration
- Nonpharmacologic therapy
  - 7 studies; only exercise demonstrated short-term improvement

Petersen, Neurology 2018

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Blood pressure control and lipid lowering does not prevent cognitive decline (HOPE-3) (9)

- Subgroup analysis of RCT of persons at least 70 at baseline
  - men at least 55 years of age and women at least 65 years of age with at least one additional clinical cardiovascular risk factor (or women at least 60 years of age with 2 additional risk factors)
  - 4-week active treatment run-in period
  - candesartan/hydrochlorothiazide 16/12.5 mg daily plus placebo (n = 593), rosuvastatin 10 mg daily plus placebo (n = 594), both active drugs (n = 587), or double placebo (n = 587)
  - Every 6 months administered 3 different standardized tests of cognition
- After 5.7 years of FU no difference in degree of change from baseline in cognition or function despite lower BP and LDL

Bosch, Neurology 2019

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Does vitamin D prevent cognitive decline in African-American women with low levels? (10)

- No

Owusu, JAGS 2019

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Does vitamin D prevent cognitive decline in African-American women with low levels? (10)

- No
- RCT
  - 260 African-American women with vitamin D levels between 8 and 26 ng/mL
  - daily vitamin D3 (2400 IU, 3600 IU, or 4800 IU based on initial Vit D levels and then titrated every 3 months to vit D level >30ng/mL) or placebo
  - Each group also received 1200 mg calcium daily
- Bad news – 74 women (32%) dropped out
- At end of 3 years, MMSE scores increased in both groups, but the net change was similar

Owusu, JAGS 2019

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Anticholinergic medications are associated with dementia and cognitive decline in the elderly (11)

- Updated SR with 26 “new” studies
  - 621,548 participants; mean duration of 73 months
  - Only 1 was at moderate ROB, the rest were worse ☹
  - Prior SR 46 smaller studies, but better quality – go figure
  - Lots of heterogeneity
- Anticholinergics associated with increased risk of developing dementia (RR raged from 1.2 to 1.5 depending on duration of use)
- No association with developing MCI (based on MMSE cutoff), however there was greater cognitive decline

Pieper, Age Ageing 2020

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Multi-domain interventions to prevent dementia and cognitive decline (12)

- Cochrane SR of 9 RCTs with 18,452 participants
  - Multi-domain interventions vs. usual care or sham
  - All reported measures of cognition (highly variable measures); only 2 reported incident dementia
  - Duration from 12 months to 10 years
- Incident dementia – 2 decent-quality studies; no difference
- Cognitive decline – variable quality studies, inconsistent results, at best small improvement that is not clinically important

Hafdi, Cochrane 2021

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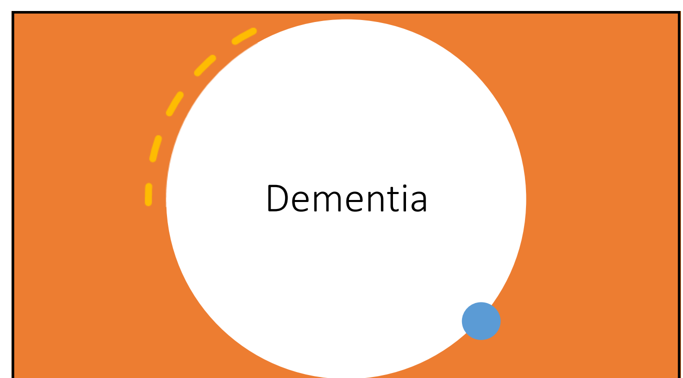

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Screening for cognitive impairment: USPSTF I recommendation (13)

- SRs
- ONE RCT (n=4005) directly assessing the effect of screening for cognitive impairment on patient-oriented outcomes
  - At 6 and 12 months, no differences in HRQOL, health care use, or measures of advance-care planning
- Screening tools – high sensitivity and specificity for detecting dementia
- Pharmacologic and non-pharmacologic treatments – disappointing
- No harms identified

USPSTF, JAMA 2020

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ASA does not decrease death, disability, and dementia in older patients (ASPREE) (14)

- RCT with 19,114 community-dwelling elders
  - no known cardiovascular or cerebrovascular disease, dementia
  - 100 mg of enteric-coated aspirin or placebo
  - 1 month placebo run-in (adherence) – 61% “failed”
- Median follow up 4.8 years
- No difference in composite of death, dementia, or physical disability
- Aspirin vs. placebo
  - Increased all-cause mortality (12.7 vs 11.1 events per 1000 person-years; NNTH = 625 per year)
  - Increased major hemorrhage (8.6 vs 6.2 events per 1000 person-years; NNTH = 417 per year)

McNeil, NEJM 2018

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Medications to improve cognition (15)

- SR of 66 RCTs that were selected because they were at low or medium risk of bias
- Cholinesterase inhibitors (mostly donepezil); 25 trials, n = 9476
  - slightly improved measures of cognitive function (SMD 0.30)
  - No improvement in overall function or global clinical impression
- Adding memantine to a cholinesterase inhibitor; 6 trials, n=2227
  - improved cognition and overall clinical impression, but not function
- Behavioral or psychological symptoms – insufficient evidence
- Harms – rates of medication withdrawal were higher than placebo (dose dependent)

Fink, Ann Int Med 2020

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Withdrawing medications in persons with dementia (16)

- If the medications to treat dementia aren’t all that helpful, what happens with we stop them?
- Cochrane SR
  - 7 trials, 759 participants
  - 6 weeks to 12 months
  - Moderate to high risk of bias
- Discontinuing treatment and cognition
  - Short term worsening (SMD -0.42)
  - Medium term – no statistically significant difference but removing 1 “odd” study eliminated the inconsistency (SMD -0.62)
  - Long term – single study – 2 points lower on MMSE
- Discontinuing treatment and function
  - Short term – no difference
  - Medium term – uncertain
  - Long term – single study, worse function - -3.38 on the Bristol ADL Scale

Parsons, Cochrane 2021

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Nonpharmacologic approaches for controlling aggression/agitation (17)

- SR of 163 RCTs
  - 23,143 patients
  - Half the studies were at high risk of bias ☹
- Compared with modifying instrumental activities of daily living
  - antipsychotics provided no additional benefit
  - Cannabinoids and dextromethorphan/quinidine were moderately more effective
- Outdoor activity, multidisciplinary care, and massage and touch therapy, with or without music were effective in producing a large reduction in aggression and agitation

Watt, Ann Int Med 2019

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Mirtazapine does not reduce agitated behaviors in persons with dementia (SYMBAD) (18)

- RCT with 204 persons with dementia **and** coexisting agitation not responding to nonpharmacologic therapy
- Randomized to 45 mg mirtazapine once daily (titrated as tolerated from 15 mg daily) or placebo
- After 12 weeks the severity of agitation improved in both groups, but no difference in degree of improvement
- No difference in caregiver burden
- More deaths (7 vs. 1)

Banerjee, Lancet 2021

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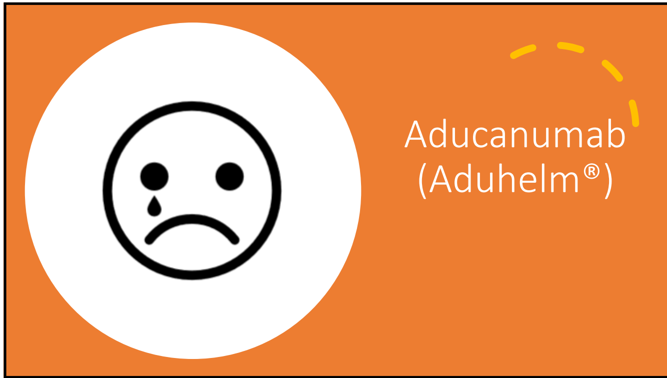

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Saga

- Approved by FDA in 2021
- Several advisory panel members resigned
- February 26, 2022 **ZERO** published trials with clinically relevant endpoints
- ClinicalTrials.gov
  - 11 studies
    - 4 completed that assess dose finding and bioavailability
    - 4 terminated for futility
    - 2 are in recruitment
    - 1 has completed recruitment and it still active (no data yet)
- The only published data so far addresses amyloid deposition

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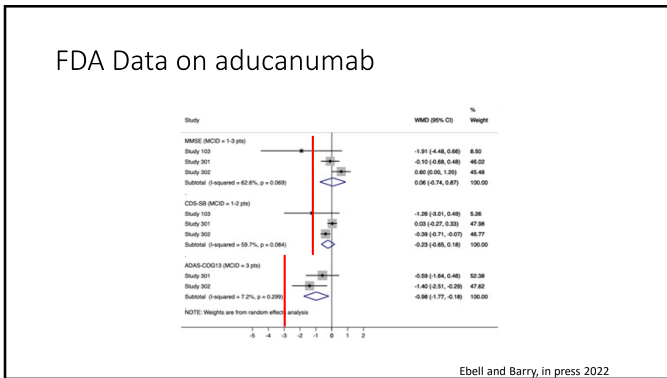

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Harms of aducanumab

- Amyloid-related imaging abnormalities (ARIA)
  - edema (35% of treated patients)
  - hemorrhage (21% of treated patients)
- ARIA associated with
  - headache (47%)
  - confusion (15%)
  - dizziness (11%)
  - nausea (8%)
- Cost – weight based, but the average initial cost was $56,000/year, but in December 2021 the manufacturer announced the maintenance dose cot will be decreased to $28,200/year
- Final decision 4/7/2022: CMS will only pay if the person is enrolled in a clinical trial

Ebell and Barry, in press 2022

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Bottom Lines

- Consider referring a patient to palliative care if you would not be surprised the person would die within a year.
- Facilitating advanced care planning and execution of advanced directives is feasible in practice and through online modules for those with access
- Up to 1/3 of persons with mild cognitive impairment will actually develop normal cognition
- Interventions to prevent dementia are disappointing (BP lowering, statins, aspirin, medications, multi-domain interventions, etc.)
- While the effectiveness of adding cholinesterase inhibitors or memantine does not seem to do much for persons with dementia, limited data suggests that withdrawing them worsens cognition and function
- So far, the newly FDA-approved drug aducanumab has no meaningful effect on measures of cognition.

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